4. (Amended) The pharmaceutical composition of claim 1, wherein the CTL activating peptide is the adenovirus-derived E1A peptide having the sequence SGPSNTPPEI (SEQ ID NO: 2), or the HPV16 E7 peptide derived from the human papillomavirus type 16, having the sequence RAHYNIVTF (SEQ ID NO: 3).

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REMARKS

I. Restriction Requirement

The Office has incorrectly indicated that "a complete reply to the final rejection must include cancellation of non-elected claims", citing MPEP § 821.01. This Office Action is not a FINAL Office Action. This section of the MPEP refers to a final rejection of the application, not a restriction requirement made final. Many times non-elected claims are maintained throughout prosecution of the application for various reasons, e.g., rejoinder. Therefore, Applicants submit that they are not required to cancel claims 8-13 at this time in order to be responsive.

II. Sequence Listing

Applicants submit a new sequence listing that includes SEQ ID NO. 3. In addition, Applicants have included the necessary statements regarding the substitute Sequence Listing and CRF, pursuant to 37 CFR § 1.821.

III. Claim to Domestic Priority Under 35 U.S.C. § 119(e)

In the Declaration filed with the Notice to File Missing Parts on November 23, 1999, Applicants requested benefit of priority to their provisional application, Serial No. 60/086,625, filed May 23, 1998. Applicants request that the Office acknowledge this request. Applicants have amended the first sentence of the specification accordingly.

IV. Rejections Under 35 U.S.C. § 112, First Paragraph

A. Claims 1-3 and 5-7 have been rejected as containing subject matter that allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time of filing. The Office alleges that Applicants' specification does not provide sufficient written description of "any CTL activating peptides other than SEQ ID NO. 2 and SEQ ID NO. 3" (Office action at page 3.)

Applicants respectfully traverse this rejection. Possession of a species that is representative of the genus is sufficient to meet the written description requirements. Following the "Decision Tree" in the Written Description Guidelines for Original Claims, if there is a representative number of species implicitly or explicitly disclosed, then Applicants have satisfied the written description requirement. Such is the case here. Applicants have implicitly disclosed the genus of compounds by defining the common functional attribute, i.e., that they be CTL-activating.

Further, even if one accepts the standard the Examiner is applying, the description is adequate. This conclusion is supported by the guidelines presented in the "Revised Interim Written Description Guidelines Training Materials." *See, e.g.,* Example 16. (Attached as Exhibit A)

As one skilled in the art knows, to be activated, a precursor T-killer cell ("pCTL") must recognize its specific antigen peptide, which is presented as MHC class I molecules on professional APC. (*See* Specification at page 2, lines 1-2.) It has been shown that protein and peptide antigens recognized by CTLs can be used to induce

pCTLs *in vivo*. Intravenous injection of antigenic MHC class I–binding peptides can specifically prime spleen T cells for subsequent *in vitro* induction of antipeptide CTLs (Carbone, et al., "Induction of ovalbumin-specific cytotoxic T-cells by *in vivo* peptide immunization", *J. Exp. Med.* 169:603-612 (1989)). Similarly, peptide pulsing of dendritic cells is capable of priming spleen cells for subsequent *in vitro* CTL induction (Porgador et al., "Bone marrow-generated dendritic cells pulsed with a class I-restricted peptide are potent inducers of cytotoxic T-lymphocytes", *J. Exp. Med.* 182:255-260 (1995)) or inducing CTLs that protect mice against tumors expressing the peptide (Celluzzi, et al. Peptide pulsed dendritic cells induce antigen-specific CTL-mediated protective tumor immunity", *J. Exp. Med.* 183:283-287 (1996)).

Applicants have discovered that administering a CD-40 binding molecule in combination with this specific antigen peptide (CTL activating peptide) to which one is trying to stimulate an immunological response can enhance this CTL activation.

To demonstrate the effect of combining a CD-40 binding molecule with a specific antigen peptide, Applicants presented evidence in Example 3 that shows an enhanced CTL-response when anti-CD40 mAb FGK-45 was administered in combination with E1A/IFA vaccine. Mice that received this combination mounted strong E1A-specific CTL responses (Figure 7b and 7e). (Specification at page 17.)

Additional evidence of this enhanced activation is presented in Example 4. Mice receiving E7 peptide (CTL activating peptide) in combination with CD40-triggering mounted a more potent CTL-response than mice treated with only the E7-peptide. (Specification at page 19.)

The discussion above illustrates that numerous peptides were known at the time the invention was made which induced antigen-specific CTL-mediated protective immunity. In view of the foregoing discussion of the prior art, one skilled in the art would have recognized that CTL-activating peptides were described in the literature. The methods for determining those antigenic portions of a particular virus, infectious agent or tumorogenic antigen for inducing CTL-activation were also known. Considering the routine art-recognized method of making antigens and antigenic fragments, the well-defined functional characteristics for the class of peptides (i.e., CTL-activating), and the fact that the CTL-mediated protective immunity is a well-defined technology, one skilled in the art would have recognized that the spectrum of antigenic peptides which elicit CTL activation were implicitly disclosed as a result of the disclosure in the specification, particularly in Examples 3 and 4.

Thus, Applicants have conveyed with reasonable clarity to those skilled in the art that, as of the filing date of the parent provisional application, Applicants were in possession of the claimed invention. Therefore, Applicants request that the rejection be withdrawn.

B. Claims 1-7 have been rejected as lacking enablement for pharmaceutical compositions comprising any CTL activating peptide or the use of said compositions to treat any tumor or infectious disease.

Applicants respectfully traverse this rejection. As discussed in Section A above, one skilled in the art would have recognized the spectrum of antigenic peptides which elicit CTL activation from the disclosure in the specification, including Examples 3 and 4.

Thus, the specification does provide an enabling disclosure for identifying CTL-activating peptides useful in the pharmaceutical composition. (*See* Example 1)

In addition, the examples presented in the specification clearly illustrate that administering CD-40 binding molecules enhances the activation of CTL–mediated response to infectious agents such as viral antigens, as well as tumor antigens.

It has been determined that interactions between T-helper cells and dendritic cells ("DC") through the CD40-CD40L binding results in activation of the DC, thereby enabling the DC to efficiently prime naive CTL. CTL activation by the CTL-activating peptide and the CD40 binding molecule, e.g., anti-CD40 antibody, should provide the same response to any infectious disease or tumor. Therefore, the specification does provide an enabling disclosure for treating tumors or infectious diseases through the activation of CTLs.

The Office alleges that the specification provides no guidance concerning the characteristics of the CTL activating peptides. However, this descriptive name in itself tells the skilled artisan the scope of peptides encompassed, i.e., CTL activating. Example 1 provides a well characterized model system for testing primary activation of CTL responses *in vivo*. The use of this method for identifying CTL-activating peptides is well within the skill of the artisan, which in this technology is high. It would not require undue experimentation to select a CTL activating peptide for a particular disease or tumor.

Treatment with antibodies and peptides is now well accepted therapy. The specification states at page 12 that the dosage of molecules can be readily determined

by extrapolation from *in vitro* tests, assays, animal experiments, or human clinical trials. This extrapolation is also within the purview of the skilled artisan.

The Office alleges at page 8 of the Office Action that it is unclear whether IFA is critical for the generation of the observed CTL response. However, Examples 1 and 2 do not use adjuvant. Moreover, at page 16, lines 14-21, of the specification clearly illustrates that adjuvant alone is not responsible for the response, otherwise there would be no difference in the data presented for E1A/IFA and E7/IFA in figure 6.

It is further noted that the Office has equated "method of treating" and "protection". Applicants have not claimed a vaccine nor have they claimed a method or preventing. The method of treating infectious diseases or tumor growth does not require complete protection.

In view of the foregoing remarks, the entire scope of the claims is fully enabled and Applicants request that the rejection be withdrawn.

V. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 4 has been rejected as indefinite because the recited amino acid sequence and its identifier do not correspond to the identifier disclosed in the specification. Applicants have amended claim 4 to correct the typographical error and request that the rejection be withdrawn as moot.

VI. Rejection Under 35 U.S.C. § 103(a)

Claims 1-7 have been rejected as unpatentable over Feltkamp et al. (Eur. J. Immunol., 23: 2242-2249 (1993)), in view of WO 96/26735.

The Office alleges that WO 96/26735 teaches "the stimulation of anti-tumor immune responses by administering anti-CD40 antibody, preferably a human momoclonal anti-CD40 antibody." (Office Action at page 11.) The Office alleges that Feltkamp et al. "teaches the stimulation of anti-tumor immune responses against HPV expressing tumors by administering an HPV E7 CTL peptide epitope, specifically disclosing the use of the epitope RAHYNIVTF to immunize mice against tumor challenge." *Id.* at pages 11-12.

The Office admits that neither reference teaches the combination of a peptide epitope with anti-CD40 antibody to treat tumors. Citing *In re Kerkhoven*, the Office concludes that because both reference teach the treatment of tumors with a composition, that "it would have been *prima facie* obvious to one of ordinary skill in the art combine these compositions to generate a new composition for the treatment of cancer with a reasonable expectation of success." (Office Action at page 12.)

Applicants respectfully traverse this rejection. Applicants submit that the Office has not provided a clear and convincing showing of how the references would have motivated one of ordinary skill in the art to combine their teachings to arrive at the claimed invention. *In re Dembiczak*, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999).

In *Dembiczak*, the court reversed the Board of Patent Appeal and Interferences, holding that claims directed to trash bags resembling jack-o-lanterns were not obvious in view of a combination of references. Before addressing the merits of the case, the

court discussed in great detail the showing required to establish a *prima facie* case of obviousness:

> Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. . . .
>
> *Id.* at 1617 (citations omitted; emphasis added).

Contrary to the Office's conclusion regarding the holding in *In re Kerkhoven*, the Federal Circuit's decision in *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987) illustrates that the suggestion to combine references must come from the references and not the Applicants' disclosure. In *Geiger*, Appellants claimed a method of inhibiting scale formation on and corrosion of metallic parts in cooling water systems by use of compositions containing (1) a copolymer of sulfonated styrene/maleic anhydride (SSMA); (2) a water soluble zinc compound; and (3) an organo-phosphorus acid compound or water soluble salt. The collective prior art taught using each of these three components, separately or in a combination for treating cooling water systems. The Board held it *prima facie* obvious to combine the three components together for their known functions and to optimize the amount of each. *Geiger* at 1277-78.

The Federal Circuit reversed the Board, emphasizing that "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *Id.* at 688, 2 U.S.P.Q.2d at 1278. The court then proceeded to go through each of the references relied on showing why, absent hindsight, the skilled artisan would not have found it obvious to make the claimed composition. While acknowledging that combining the three components of the claimed composition may have been obvious to try, the court stated it does not constitute the standard for combining references under § 103.

As is evident from the general statements of the reasoning underlying the rejection, no particular suggestion, teaching, or motivation to combine the references is identified by the Office. No factual findings that might serve to support a proper obviousness analysis are provided. Instead, the Office merely discusses a way that the cited references can be combined to read on the pending claims. This is not a clear and particular showing, that is, actual evidence, that the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art in view of the teaching of the cited references. Under the precedent set forth in *Dembiczak*, as well as the other reasons expressed herein, the Office has failed to establish a *prima facie* case of obviousness. The mere fact that references can be combined or modified does not render the resulting combination obvious unless the prior art also suggests the desirability of the combination. M.P.E.P. 2143.01, *citing In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Accordingly, this rejection under 35 U.S.C. 103(a) is improper and should be withdrawn.

Even if, for the sake of argument, the references were to be combined, there is no suggestion of the superior results obtained by the combination of CD-40 binding molecule and the CTL activating peptide. Figure 8 and Example 4 clearly illustrate these superior results. Administration of HPV 16 E7 peptide in combination with an injection of the anti-CD40 Ab markedly reduced tumor growth and 7 out of 10 mice rejected the tumor. Whereas, when mice were injected with HPV 16 E7 peptide alone (open squares), most animals succumbed to the tumor.

In addition, Example 3 illustrates that the administration of anti-CD40 antibody can overcome systemic CTL-tolerance associated with the injection of Ad5E1A-derived peptide.

Neither of the cited prior art references teaches or suggests this enhancing effect that CD40 binding molecule has on CTL-activating peptides. Therefore, for this additional reason, the rejection should be withdrawn.

Conclusion

In view of the foregoing amendments and remarks, Applicants request timely allowance of the pending claims.

Respectfully Submitted,

Dated: April 3, 2001.

BY: Cheryl A. Liljestrand
Cheryl A. Liljestrand
Reg. No. 45,275

Mailing Address:
Tanox, Inc.
10301 Stella Link Rd
Houston, TX 77025
(713) 578-4000

Marked up Version of the Amended Claim in Compliance with 37 C.F.R. § 1.121(c)(1)(ii):

4. (Amended) The pharmaceutical composition of claim 1, wherein the CTL activating peptide is the adenovirus-derived E1A peptide having the sequence SGPSNTPPEI (SEQ ID NO: [1] 2), or the HPV16 E7 peptide derived from the human papillomavirus type 16, having the sequence RAHYNIVTF (SEQ ID NO: 3).